Tetrahedron Letters,Vol.24,No.26,pp 2697-2700,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

AN ECONOMICAL DIELS-ALDER STRATEGY FOR THE SYNTHESIS OF DAPHNIPHYLLUM ALKALOIDS

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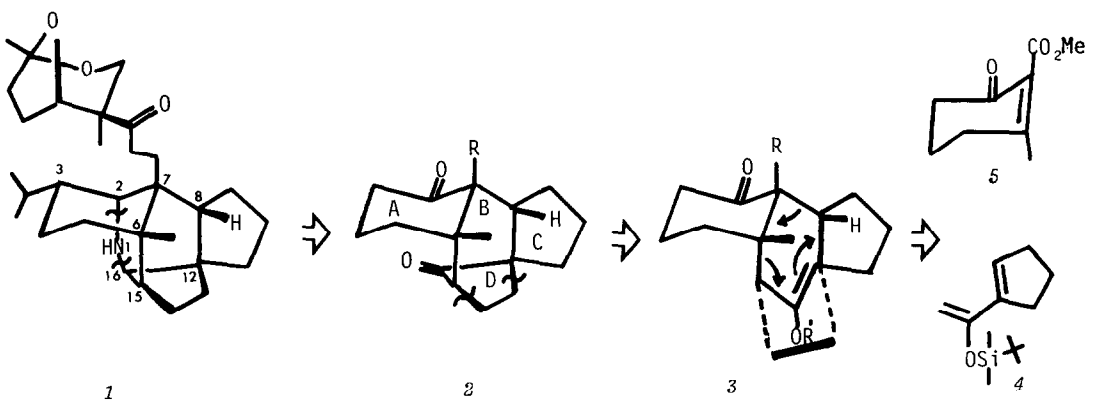
SUMMARY: A convergent and essentially self-consistent strategy, featuring an unusual Diels-Alder reaction has been devised for the stereo-controlled synthesis of a logical tetracyclic precursor *21* to daphniphyllum alkaloids.

In this Letter we describe an economical strategy[1] for the stereo-controlled synthesis of a logical tetracyclic precursor (*viz 21*) to the physiologically interesting and structurally complex daphniphyllum alkaloids.[2] The strategy was derived through a general retrosynthesis analysis of secodaphniphylline[3] *1* (*1*⇒*2*⇒*3*⇒*4*+*5*) that indicated a Diels-Alder reaction between the siloxy diene *4* and 2-carbomethoxy-3-methylcyclohexenone *5*.[4]

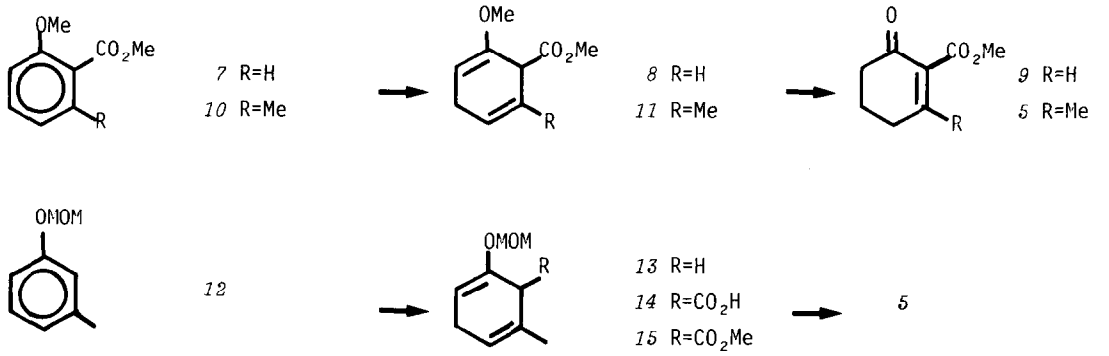


1 *2* *3* *4*

Simple 2-cyclohexenones are notoriously poor dienophiles in the absence of Lewis acids,[5] but we reasoned that the 2-carboxy substituent in *5* would enhance dienophilicity and counterbalance the increased steric demand for the transition state. A regioselective, suprafacial, endo addition[6] under thermal conditions, would generate a tricyclic keto ester (*viz 18*) with not only the desired relative chirality at C6, C7, and C8 but also a silyl enol ether group for a subsequent regio- and stereo-controlled delivery of a D-ring precursor to C12 (c/f *2*⇒*3*). However, the lack of adequate precedents for the desired Diels-Alder step suggested that we should also examine the [4+2]-cycloreactivity of diene *4* with potentially useful dienophiles lacking a C3-methyl group, e.g. cyclohexenone *9*.[7] Consequently, our primary synthesis objectives became *4*, *5*, and *9*.

Diene *4*[8] was first prepared, from 1-acetylcyclopentene *6*[9] using standard conditions for kinetic enolate formation and trapping, viz LDA (1.2 eq) then t-$BuMe_2SiCl$ (1.3 eq), but the isolated yield using this method rarely exceeded 26%. We found, however, that *4* could be made more conveniently and in higher yield (61%) by adding KH (5 eq) to a THF solution of *6*

containing t-$BuMe_2SiCl$ (1.5 eq). Work-up simply involved filtration through Florisil, concentration, and bulb-to-bulb distillation.

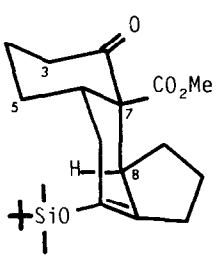


Enone *9* was made efficiently through Birch reduction (K, NH_3, THF, t-BuOH) of 2-methoxy methylbenzoate *7*[10] then hydrolysis [1MHCl/THF(1:1), Δ, 1h] of the enol ether *8*, with concomitant conjugation of the olefinic bond. The 3-methylcyclohexenone *5* could be prepared via *11* in an analogous way, but the synthesis of aromatic precursor *10* was protracted and inefficient.[11]

In a new and more direct approach to *5*, the MOM ether *12* derived from *m*-cresol (CH_3OCH_2Cl, Hünig's base, THF, 25°, 17h) was first reduced (Li, NH_3, THF, tBuOH) and the resulting dihydroaromatic ether *13* carefully lithiated (nBuLi-TMEDA, 1.5 eq, -30°, 3.5h), then carboxylated (CO_2, -78°); finally, the acid *14* was methylated (CH_3I, 10 eq, K_2CO_3, acetone, 25°, 8h) and the MOM enol ether *15* hydrolysed to *5*[8] as for *11* above. It is noteworthy that the site of MOM-assisted lithiation in *13* is regio-complementary to that for the corresponding aromatic ether *12*, where attack is selective for the less hindered C6-ortho position.[12]

With the required Diels-Alder substrates in hand, we examined first the reactivity of the less-substituted enone *9* (1 eq) with diene *4* (1 eq). In refluxing benzene, two separable adducts (MPLC) were formed (22h, 62%) in a ratio 1:3 which could be designated as exo[αH(8)]-*16*[8] and endo[βH(8)]*17*[8] respectively: in particular, conformational analysis based on Dreiding models revealed that the endo adduct has an exposed convex β-face, whereas the exo adduct has the α- and β-faces more equally exposed, i.e. the ester group is relatively more hindered. Consequently, in ^{1}H-nmr spectra, the β-carbomethoxy group shows a greater ASIS (CCl_4 *vs* C_6D_6)[13] upfield for the endo isomer *17* (0.44 ppm) than for the exo isomer *16* (0.27 ppm). Moreover, in the ^{13}C-nmr spectra ($CDCl_3$), γ-gauche effects on C8 are experienced from C3 and C5 in the exo isomer *16* (δ40.5) but not in the endo isomer *17* (δ47.9). These data are consistent with the indicated conformations for the *cis*-octalone A/B-ring moieties in *16* and *17*, which tend to minimize steric interactions, particularly along the C7-C8 bond.

The facile and predominant formation of endo adduct *17* was encouraging for the crucial Diels-Alder reaction between the enone *5* and diene *4*. This was achieved by heating the reagents (equi-molar) at 140° for 66h in a dry, base-washed glass tube which had been purged of oxygen, evacuated, then sealed. MPLC easily separated starting materials from an adduct (20%) which had spectroscopic characteristics entirely consistent with the desired endo [βH(8)] structure *18*.[8]



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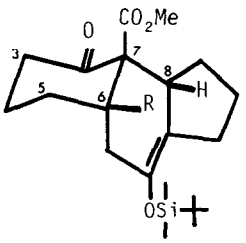
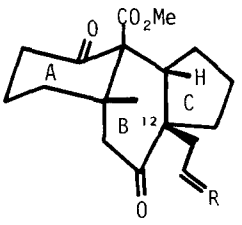


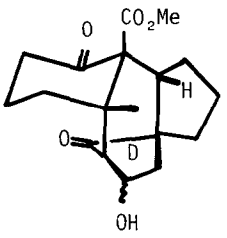
17 R=H

18 R=Me



19 R=CH_2

20 R=O



21

Next, the elements of the D-ring were introduced stereo- and regio-selectively into *18* through fluoride-mediated alkylation with allyl bromide ($nBu_4\overset{+}{N}F^-$, THF, -15°, 0.5h) to give the olefin *19*.[8,14] A computer-generated perspective drawing (FIGURE 1) from single-crystal X-ray analysis of *19* substantiated our structural assignments and showed the C12 allyl group disposed axially to a boat-conformed B-ring.[15] Therefore, we correctly predicted that the

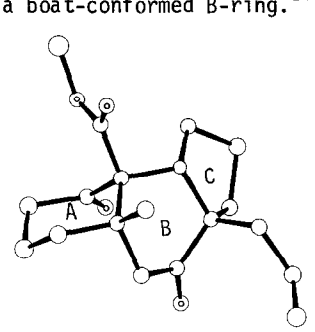


FIGURE 1: Computer-generated perspective drawing of *19* based on X-ray data; hydrogen atoms have been omitted for clarity.[15]

derived intermediate aldehyde *20*[8] (O_3, EtOH,CH_2Cl_2; Zn-HOAc) would readily undergo the desired aldol cyclization ($nBu_4\overset{+}{N}F^-$, THF, 25°) to close the D-ring and, in this final step, complete the main carbocyclic framework *21*[8] of secodaphniphylline *1*.

Clearly, the economy of our strategy for daphniphyllum alkaloid synthesis is derived from: (1) the convergency, *i.e.* *4* + *5* (2) the self-consistency[1] *i.e.* after each C-C bond construction, the residual functionality is correctly sited for the next construction and (3) the stereochemical control. Thus, the required four rings and five contiguous asymmetric centres of *21* are assembled in just four steps. We note parenthetically that the regio-controlled (C2) lithiation of dihydroaromatic ether *13*, and the improved preparation and fluoride-mediated alkylation of *t*-butyldimethylsilyl enol ethers, are methodologies with a wider potential in synthesis. Accordingly, these are currently under investigation in parallel with the elaboration of *21* towards secodaphniphylline *1*.

ACKNOWLEDGEMENTS: We are grateful to Mr G.M. McLaughlin for X-ray structure determination, to Professor L.N. Mander for encouragement, and for a Commonwealth Postgraduate Research Award to J.O.

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3. Secodaphniphylline [12(1→16)*abeo*-Daphnane numbering] is considered to be the central biosynthetic precursor to diterpenoid alkaloids constituting the daphniphyllum class.[2]

4. The possibility of utilizing a 6-isopropyl analogue of *5*, derived from a chiral building block, is also under examination.

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6. Endo addition and therefore βH(8) stereochemistry was not a certainty, however, since molecular models revealed that the diene could undergo secondary orbital overlap with the ester carbonyl group during an exo transition state. Nevertheless, in the endo mode, the ketone can interact and this was expected to dominate.

7. A recent communication [H-J Liu and T.K. Ngooi, Synth. Commun., 12, 715 (1982) states that *9* is a poor dienophile under thermal conditions and advocates stannic chloride catalysis. This is contrary to our findings that *9* reacts readily with *4* at 1 bar; moreover, such catalysis would be incompatible with the survival of the strategically important silyl enol ether group in adducts *17* or *18*. The application of pressure to improve the yields of *17* and *18* is under investigation.

8. All new compounds gave satisfactory elemental analyses (combustion or HRMS) and had consistent spectroscopic characteristics; selected data are: *4*, bp 105°/0.5mm; IR(film) 1632 (m), 1588 (s) cm^{-1}; ^{1}H-nmr (CCl_4) δ 0.15 (s, 6H), 0.95 (s, 9H), 4.15 (s, 2H), 5.88 (brs, 1H). *5*, bp 140°/1mm; IR(film) 1735, 1673, 1635 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.03 (s, 3H), 2.13 (m, 2H), 2.45 (m, 4H), 3.83 (s, 3H). *16*, mp 71-72°, ^{1}H-nmr δ (CCl_4) 3.62, (C_6D_6) 3.35, OMe. *17*, mp 77-79°; ^{1}H-nmr δ (CCl_4) 3.74, (C_6D_6) 3.30, OMe. *18*, mp 76.5-77°; ^{1}H-nmr δ (CCl_4) 3.65, (C_6D_6) 3.25. *19*, mp 99-101°; ^{1}H-nmr ($CDCl_3$) δ 1.32 (s, 3H), 3.75 (s, 3H), 5.05 (m, 2H), 5.77 (m, 1H). *20*, ^{1}H-nmr ($CDCl_3$) 1.29 (s, 3H), 3.76 (s, 3H), 9.88 (t,J = 2.4Hz, 1H); MS $^m/_z$ 320 (M, 49%), 302 (M-H_2O, 23%), 292 (M-CO, 26%), 278 (M-CH_2CO, 33%), 169 (100%). *21*, IR ($CDCl_3$) 3690 (free OH), 3600 (bonded OH), 1745 (sh), 1730 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.02 (s, 3H), 3.70 (s, 3H), 4.40 (t,J = 7Hz, HCOH, stereochemistry undefined); MS $^m/_z$ 320 (M, 100%), 302 (M-H_2O, 41%), 274 (302-CO, 44%).

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13. E.M. Engler and P. Laszlo, J. Amer. Chem. Soc., 93, 1317 (1971).

14. The stereochemistry at C12 follows from the expected attack by allyl bromide to the convex β-face of fluoride-activated *18*. By analogy, endo adduct *17* also gave a single isomer, whereas the more planar exo adduct *16* afforded a mixture of C12 epimers.

15. *Crystal data for 19* $C_{19}H_{26}O_4$, M_r = 318.4, Space group $P2_1/n$, a = 18.622(6), b = 7.428(3), c = 12.499(4) Å, β = 104.17(1)°, V = 1676.3 Å^3, Dc = 1.26 Mgm^{-3}, Z = 4, CuKα radiation, λ = 1.5418Å, μ = 0.665 mm^{-1}, T = 293(1)°K, R = 0.036, Rw = 0.039, 1984 unique reflections. Refined coordinates and bond distances have been supplied for the C.C.D.C.

(Received in UK 18 April 1983)